REMARKS

Upon entry of this amendment, claims 1-2, 4, 10 and 12-17 will be pending in this application. Claims 1-2, 4, 10 and 12-13 are amended. Claims 3, 5-9 and 11 are canceled without prejudice. Applicants reserve the right to pursue canceled subject matter in one or more continuing applications. Claims 14-17 are new. Support for claims 14-16 can be found in claim 3 as originally filed. Support for claim 17 can be found in claim 11 as originally filed. No new matter is added by these amendments.

Applicants' response to the Examiner's Official Action is as follows.

Lack of Unity

The Examiner has required restriction of the claims under 35 U.S.C. §121 and 372 to one of the following groups.

I. Claims 1-3 and 10-13, drawn to compounds of Formula I, wherein X and Y are each carbon, classified in class 544, subclasses 8, 238, 315 and 405, and class 546, subclasses 157, 159, 160 and 167, pharmaceutical compositions thereof and therapeutic methods using these compounds, classified in class 514, subclasses 222.5, 252.04, 255.05, 269, 312, 313 and 314.

II. Claims 1-4 and 10-13, drawn to Formula I compounds, where X is carbon and Y is nitrogen, classified in class 544, subclasses 8 and 284, pharmaceutical compositions and therapeutic methods using these compounds, classified in class 514, subclasses 222.5, 252.02, 255.05, 266.21, 266.23 and 266.1.

III. Claims 1-4 and 10-13 drawn to compounds of Formula I wherein X is nitrogen and Y is -CR7, classified in class 544, subclasses 8, 238, 315 and 405, class 546, subclasses 157, 159, 160, and 167, pharmaceutical compositions and therapeutic methods using these compounds, classified in class 514, subclasses 222.5, 252.04, 255.05, 269, 312, 313, and 314.

IV. Claims 1-5 and 10-13, drawn to Formula I compounds, where X and Y are both nitrogen and a process for preparing them, classified in class 544, subclasses 8,

238 and 279, pharmaceutical compositions and therapeutic methods using these compounds, classified in class 514, subclasses 222.5, 252.04, 255.05 and 269.

In a telephone conversation with the Examiner on October 4, 2007, Applicants made a provisional election, with traverse, to prosecute the invention of Group IV, claims 1-5 and 10-13. Applicants affirm the election of Group IV but are withdrawing the original election with traverse and are now electing Group IV without traverse. Applicants have amended claims 1-5 and 10-13 to remove non-elected subject matter from these claims.

Rejections Under 35 USC 112, first paragraph

The Examiner has rejected claims 11-13 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for CFR binding activity *in vitro* and CFR functional assay *in vivo*, allegedly it does not reasonably provide enablement for treatment of any condition mediated by CFR (claim 11), or where the condition is depression or anxiety (claim 12), or IBS or IBD (claim 13). According to the Examiner, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Solely in order to expedite prosecution and without in any way conceding to the propriety of the rejection, Applicants have canceled claim 11 and amended claim 13 to recite only methods of treating IBS. Applicants respectfully traverse the rejection with regard to claim 12 and amended claim 13.

Applicants assert that, at the time of filing, it was known in the art that CRF plays a role in depression, anxiety and IBS and that CRF receptor antagonists could be useful in treating these three conditions. The specification teaches how to test the compounds of the instant invention for CRF receptor antagonist activity and gives dosage ranges that would be appropriate for use in the treatment of CRF mediated conditions. Given the established link between CRF and these three conditions along with the assays and dosages taught in the specification, Applicants submit that one of ordinary skill in the art could practice the methods of claims 12 and 13 without undue experimentation.

With regard to depression and anxiety, Applicants assert that it was known, at the time of filing, that CRF is hypersecreted in patients with depression and that a CRF receptor antagonist could be useful in treating depression. (Specification, page 1, lines 19-21 and Gillian *et al.*, page 1646, section Clinical Investigations, subsection A (enclosed)). According to Gillian, "Small molecule CRF_1-selective receptor antagonists may be potential anxiolytic and antidepressant agents based on published preclinical data. The available clinical data on CRF function in humans strongly suggests antidepressant potential for CRF antagonists." (Gillian *et al.*, page 1654, first column, last paragraph). Zorrilla (cited by the Examiner) also supports the link between CRF and anxiety because it gives *in vivo* results showing treatment with antalarmin (a CRF receptor antagonist) blocked CRF and novelty induced anxiety like behavior in animal models of anxiety. (Zorrilla *et al*,. page 193 Discussion). Results from an open label clinical trial showed that a small molecule CRF antagonist (R121919) significantly reduced depression and anxiety scores in patients with major depression. (Zobel, *et al.*, Abstract and page 179 last paragraph through the end of page 180 (enclosed)). These three publications all give preclinical data showing CRF is linked to depression and anxiety and that CRF receptor antagonists could be useful in the treatment of these two conditions. The strength of these preclinical data was so strong that it led to the clinical testing of a CRF receptor antagonist in humans. Thus, at the time of filing, it was known and accepted in the art that CRF receptor antagonists could be useful in the treatment depression and anxiety.

With regard to IBS, Applicants assert that it was also known, at the time of filing, that CRF plays a role in mediating the effects of stress on the gastrointestinal tract. According to Burks, an antagonist to CRF blocks the effects of stress on intestinal function and concludes that such an antagonist can be used as an effective treatment of stress-related functional bowel disease. (Burks *et al.*, column 2, lines 11-22 (enclosed)). To support this conclusion, Burks gives, in Examples 5, an assay showing that when alpha-helical CRF-(9-41) (a CRF antagonist) is administered to a rat prior to being stressed, the CRF antagonist significantly diminishes the stress-induced increases in colonic transit or fecal excretion. (Burks *et al.*, column 6, lines 16-21 and Example 5 columns 8-9). Tache (cited by the Examiner) also gives extensive preclinical data supporting the link between CRF receptor antagonism and the treatment of IBS. Given this extensive preclinical data, Applicants submit that the link between CRF receptor antagonism and the treatment of IBS was known in the art at the time of filing.

The publications discussed above show CRF plays a role in depression, anxiety and irritable bowel disorders and that CRF receptor antagonists could be useful in the treatment of these conditions. Given this link between CRF and these conditions, all one of ordinary skill in the art would need to do is test the compounds of formula (I) to determine the level of antagonistic activity that these compounds have. The specification provides two assays that one of ordinary skill in the art can use to evaluate compounds of formula (I). Applicants have given in Example 4 of the specification a CRF Binding Activity assay. One of ordinary skill in the art can use this assay to determine the binding affinity of a compound of formula (I) to both CRF_1 and CRF_2 receptors. On page 15 of the specification are the results of compounds tested using the assay described in Example 4. Applicants have also given in Example 5 of the specification, a CRF functional assay that one of ordinary skill in the art can use to determine the inhibitory (antagonistic) effect of a compound of formula (I). As for testing in animal models, many animal models were published and known in the art. Thus, one of ordinary skill in the art could test the compounds of the instant invention without undue experimentation.

In terms of dosage, Applicants have given on page 21 of the specification, typical daily dosage ranges that can be used in the treatment of depression, anxiety and IBS. Zobel also gives dosages that can be used in patients with depression (diagram on page 173). These dosage ranges give enough guidance so that one of ordinary skill in the art can practice the methods of claims 12 and 13.

Applicants assert that the specification is enabled for a method of treating depression, anxiety and irritable bowel disorders. It was well known, at the time of filing, that CRF receptor antagonists could be useful in the treatment of depression, anxiety and irritable bowel disorders. This knowledge, coupled with the CRF binding/functional assays and dosage ranges provided in the specification, allow one of ordinary skill in the art to practice the methods of claims 12 and 13 without undue experimentation.

The Examiner has rejected claims 1-5 and 10-13 under 35 U.S.C. §112, first paragraph, because the specification while being enabling for pharmaceutically acceptable salts and stereoisomers of the Formula I compounds, allegedly does not reasonably provide enablement for pharmaceutically acceptable solvates and prodrugs. Solely in order to expedite prosecution and without in any way conceding to the propriety of the rejection, Applicants have amended claims 1-2, 4, 10 and 12-13 to remove solvates and prodrugs from the claims.

In light of the above amendments and remarks, Applicants respectfully request that the rejection of claims 1-5 and 10-13 under 35 U.S.C. §112, first paragraph be reconsidered and withdrawn.

Rejections Under 35 USC 112, second paragraph

The Examiner has rejected claims 1-5 and 10-13 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

According to the Examiner the plural recitation of "A compound, including stereoisomers" in claim 1 reads on unsupported mixtures of the inventive compounds and should be singularized. Applicants have amended claim 1 as suggested by the Examiner.

According to the Examiner, the recitation of "a prodrug" in claims 1-4 and 10-13 fails to define the parent compound from which the prodrug is intended to be formed. Applicants have removed the word "prodrug" from the claims thus rendering the rejection moot.

According to the Examiner the recitation of "a suitable amine," "a suitable protecting group," "a suitable oxidizing agent," "a suitable reducing agent," "a suitable leaving group," and "the suitable reactive -Z-W derivative," in claim 5 fails to define the intended reaction when there is no definition of the conditions to which the recited reagent is to be "suitable." The Examiner further states that the recitation of "the usual conditions," fails to define the intended reaction when there is no definition of the conditions considered "usual." The Examiner also states that the phrase "preferably chloride" renders the claim indefinite because it is unclear whether the preferred limitation is part of the claimed invention. Applicants have canceled claim 5 and re-written the process of claim 5 in new claim 14, thus rendering the rejection moot.

In light of the above amendments and remarks, Applicants respectfully request that the rejection of claims 1-4 and 10-13 under 35 U.S.C §112, second paragraph be reconsidered and withdrawn.

Objected Claims

The Examiner has objected to claims 1-5 and 10-13 as directed to both elected and non-elected subject matter. The Examiner states that the claims should be amended to recite only elected subject matter. Since Applicants have withdrawn their original election with traverse and

are now electing the invention of Group IV without traverse, Applicants have amended the claims such that they recite only elected subject matter.

Conclusion

This reply is intended to further this case to allowance by addressing each ground of objection and rejection in the Examiner's Office Action. Reconsideration of this application is respectfully requested. Authorization is hereby granted to charge any fees which may be required by this paper to Deposit Account No. 19-2570. Should the Examiner have any questions regarding this application, the Examiner is invited to call the undersigned agent at the number given below.

Respectfully submitted,

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